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Sutton, Michael Edward

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Duct-to-duct biliary reconstruction in liver transplantation for primary sclerosing cholangitis is associated with less biliary complications, compared with Roux-en-Y hepatico-jejunostomy.



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M.E. Sutton
R.D. Bense
T. Lisman
E.J. van der Jagt
A. P. van den Berg
R. J. Porte

(manuscript submitted)

ABSTRACT

Background

There is no consensus on the preferred type of biliary reconstruction in patients undergoing orthotopic liver transplantation (OLT) for primary sclerosing cholangitis (PSC). Aim of this study was to compare long-term outcome after OLT for PSC using either duct-to-duct anastomosis or Roux-en-Y hepatico-jejunostomy for biliary reconstruction.

Methods

In a consecutive series of 98 adult patients undergoing OLT for PSC, 45 underwent duct-to-duct and 53 a Roux-en-Y biliary reconstruction. Median follow up was 8.2 years (interquartile range 3.9 – 14.5 years). Outcome was compared between the two groups.

Results

There were no significant differences in patient demographics and general surgical variables between groups. Overall patient and graft survival rates were similar in the two groups. The incidence of biliary strictures and biliary leakage within one year after transplantation did not differ among the two groups. However, significantly more patients in the Roux-en-Y group suffered at least one episode of cholangitis within the first year (9% in duct-to-duct versus 25% in Roux-en-Y group; $p=0.04$). In addition, Roux-en-Y reconstruction was associated with a significantly higher rate of late onset (>1 year posttransplant) nonanastomotic biliary strictures compared to duct-to-duct reconstruction (24% versus 7%, at 5 years and 30% versus 7% at 10 years; $p=0.01$).

Conclusion

Duct-to-duct biliary reconstruction in patients with PSC is associated with lower incidences of posttransplant cholangitis and late-onset non-anastomotic biliary strictures, compared with Roux-en-Y hepatico-jejunostomy. If technically and anatomically feasible, duct-to-duct anastomosis should be the preferred technique of biliary reconstruction in patients undergoing OLT for PSC.

INTRODUCTION

Primary sclerosing cholangitis (PSC) is a progressive disease that causes chronic inflammation and fibrosis of the intra- and extrahepatic bile ducts. During progression of the disease complications such as cholestasis, recurrent cholangitis and the formation of biliary strictures occur frequently (1). To date, no therapeutic option is available to halt disease progression and the only effective option for patients with end-stage PSC is orthotopic liver transplantation (OLT). Although the exact etiology of PSC remains unclear, an immune mediated cause is likely, which is supported by the observation that PSC may recur in the donor liver after transplantation (2, 3).

The mainstay of biliary reconstruction in human liver transplantation is a duct-to-duct anastomosis, in which the bile duct of the liver graft is connected to the recipient's native bile duct. However, in case of large disparity between recipient and donors bile duct size, surgeons tend to deviate from duct-to-duct anastomosis and different techniques such as Roux-en-Y hepatico-jejunostomy and choledocho-duodenostomy are used. Another indication to deviate from a duct-duct anastomosis is when there is diminished viability of the native extrahepatic bile duct or reduced patency due to inflammation and strictures as in PSC.

For years the preferred method of choice of biliary reconstruction in patients with PSC has been Roux-en-Y hepatico-jejunostomy because PSC affects the entire biliary tract and is associated with an increased risk of development of cholangiocarcinoma (4-6). Therefore, the rationale was to excise as much as native bile duct as possible in order to diminish potential complications (7). However, formal evidence that Roux-en-Y hepatico-jejunostomy is superior in patients with PSC is lacking and its routine use in these patients has been challenged (8-11). In addition, Roux-en-Y hepatico-jejunostomy is associated with disadvantages due to loss of the sphincter of Oddi, which normally prevents unsterile intestinal content from reaching the sterile biliary tract (12, 13). This makes patients after hepatico-jejunostomy more prone for ascending cholangitis. On the other hand, duct-duct anastomosis may make PSC patients more prone for late complications due to disease progression (i.e. biliary strictures) or even development of cholangiocarcinoma in the native distal bile duct (7). Until now, no consensus has been reached regarding the preferred method of biliary reconstruction in patients with PSC and although our center and others have previously shown that duct-duct anastomosis can be performed safely in selected patients with PSC undergoing OLT, data on long-term outcomes

are sparse (14). This study aimed to compare long-term outcomes after OLT in patients with PSC, who received either a duct-duct anastomosis or a Roux-en-Y hepatico-jejunostomy for biliary reconstruction.

METHODS

Patients

Between January 1, 1991 and December 31, 2011 a total of 881 OLTs were performed at the University Medical Center Groningen. Of these, 109 transplantations were performed in patients with PSC. After the exclusion of pediatric recipients (<18 years) and patients receiving a reduced graft, a total of 100 transplants resulted. Two patients were excluded because a choledocho-duodenostomy was performed yielding a total of 98 adult patients receiving a full sized liver graft with either duct-to-duct anastomosis (n=45) or Roux-en-Y hepatico-jejunostomy (n=53) for biliary reconstruction. Mean and median duration of follow-up was 8.6 ± 6.0 years and 8.2 years, respectively (interquartile range 3.9 – 14.5 years).

Clinical variables were obtained retrospectively from a prospectively collected database and missing data was obtained from the original, electronic medical records. This study was conducted in accordance with Dutch legislation and local ethical committee guidelines.

Study Variables and Outcome Parameters

Patient demographics, donor variables, surgical variables, and postoperative complications were assessed. Complications were defined as any event that required hospitalization, surgical reintervention, or endoscopic intervention. Anastomotic strictures were defined as an isolated stricture at the biliary anastomosis and a non-anastomotic biliary stricture (NAS) as any stricture, dilatation or irregularity of the intra- and extrahepatic bile ducts of the liver graft, located at other sites than the anastomosis. No attempts were made to distinguish recurrent PSC from other causes of NAS. All cases of NAS were categorized into early NAS (≤ 1 year after transplantation) or late NAS (> 1 year after transplantation). An episode of cholangitis was defined as hospital admittance with fever in which the diagnosis cholangitis was made (based on laboratory results, liver function and imaging) and the patient was treated with antibiotics. Occurrence and localization of cholangiocarcinoma were noted. Patient survival was defined as the time interval between date of OLT and patient death. Graft survival was defined as the time between OLT and retransplantation or death.

Choice of Biliary Reconstruction:

In our center, the choice between a duct-to-duct anastomosis and a Roux-en-Y hepatico-jejunostomy in patients transplanted for PSC is based on (1) preoperative imaging of the biliary tract, (2) a fresh frozen section light microscopy of the native extrahepatic bile duct, and (3) intraoperative assessment of patency of the native bile duct by antegrade passage of a biliary probe into the duodenum. If the transplant surgeon has no concerns for biliary flow impairment or (pre-) malignancy based on these findings, the method of first choice is a duct-to-duct anastomosis. Only severe dysplasia and/or significant narrowing of the bile duct are reasons to perform a Roux-en-Y hepatico-jejunostomy (14). When histological evidence of a cholangiocarcinoma is found incidentally in the frozen section analysis a pancreatoduodenectomy is performed.

Statistical analysis

Continuous variables are expressed as median and interquartile ranges and groups were compared using the Mann-Whitney U test. Categorical variables are expressed as numbers and percentages and the Chi-square test was used to compare groups. Graft and patient survival and complication free survival were estimated using the Kaplan-Meier method and groups were compared using the log rank test. P-values <0.05 were considered significant. Statistical analysis was performed using SPSS software version 19.0 for Windows (SPSS Inc., Chicago IL, USA).

Table 3.1 Donor and Recipient Characteristics and Surgical Variables

	Duct-to-Duct (n=45)	Roux-en- Y (n=53)	P-value
Donor Variables*			
Type of donor			0.12
Donation after cardiac death	8 (18%)	4 (8%)	
Donation after brain death	37 (72%)	49 (92%)	
Age (years)	41 (33 – 51)	41 (25 – 53)	0.78
Gender			0.17
• Male	56 %	51%	
• Female	44 %	49%	
Gender mismatch (donor-recipient)			0.86
• Female – male	12 (27%)	15 (29%)	
• Male – female	4 (9%)	6 (12%)	
Recipient variables			
Age (years)	45 (33 – 52)	53 (36 – 54)	0.56
Gender			0.82
• Male	34 (76%)	39 (74%)	
• Female	11 (24%)	14 (26%)	
Occult cholangiocarcinoma in explant	1 (2%)	3 (6%)	0.39
Surgical variables			
Warm ischemia time (min)	70 (49 – 70)	50 (43 – 130)	0.73
Cold ischemia time (min)	669 (396 – 908)	671 (305 – 900)	0.75

* continuous variables are presented as median and interquartile range, categorical variables are presented as numbers and percentage.

RESULTS

Duct-to-duct anastomosis was performed in 45 patients and Roux-en-Y hepatico-jejunostomy in 53 patients. There were no significant differences in baseline donor and recipient characteristics and surgical variables (Table 3.1). In two patients an initial duct-to-duct anastomosis had to be converted into a Roux-en-Y hepatico-jejunostomy; in one case after 9 months and in the other case after 41 months. In both cases the indication for conversion to Roux-en-Y hepatico-jejunostomy was recurrent cholangitis based on strictures affecting the extrahepatic bile duct. In accordance with the principle of intention-to-treat analysis, both patients were kept in the original duct-to-duct group for further analysis.

Patient and Graft Survival

Patient and graft survival data are presented in Figure 3.1. Actuarial 1, 3 and 5 year patient survival rates were 96%, 90% and 88% respectively for the duct-to-duct group and 96%, 96% and 96%, respectively in the Roux-en-Y group ($p=0.10$). Corresponding actuarial 1, 3 and 5 year graft survival rates were 93%, 86% and 79% in the duct-to-duct group and 93%, 84% and 82% in the Roux-en-Y group, respectively ($p=0.32$). Twelve patients died with a functioning graft, which was considered as an event in the graft survival analysis. Three of these patients died due to malignant disease; one glioblastoma, one patient had metastatic pancreatic cancer and one patient developed de novo cholangiocarcinoma (described below). In four cases cholangiocarcinoma was found incidentally in the explanted liver. Of these, three patients remained recurrence-free during follow-up. One patient died 7 months posttransplant with a high suspicion for metastatic disease (high levels of CA19.9 and enlarged hilar lymph nodes). Three patients died secondary to liver cirrhosis; in one case due to recurrent hepatitis B virus and in two cases of unknown etiology. Other causes of death included cardiac failure ($n=2$), upper gastrointestinal hemorrhage and hemorrhagic shock ($n=1$), traumatic accident ($n=1$), and in one case the cause of death remained unknown.

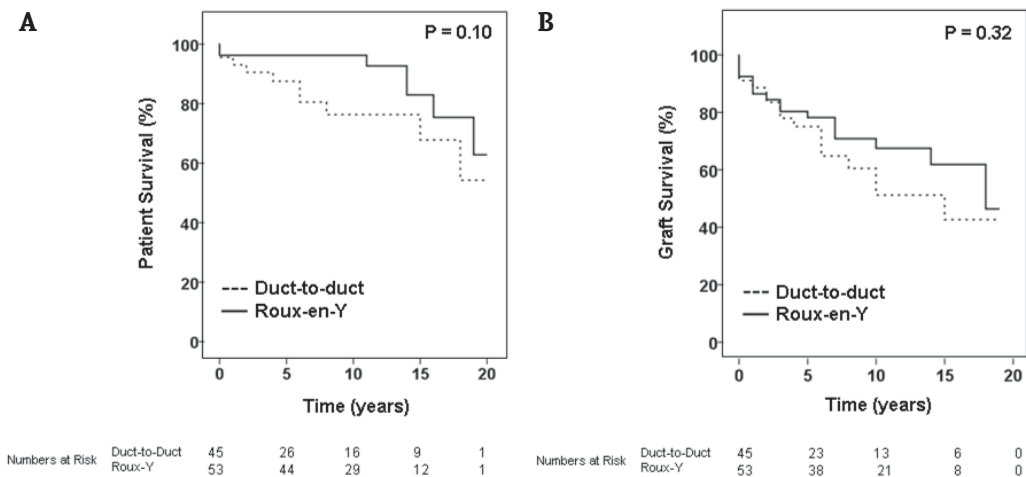


Figure 3.1. Kaplan-Meier curves comparing (A) overall patient survival and (B) overall graft survival of patients transplanted with an orthotopic liver graft for PSC in two categories based on the method of biliary reconstruction. Groups were compared using the log rank test.

Biliary Complications

An overview of all biliary complications is given in Table 3.2. A significantly higher percentage of patients in the Roux-en-Y group suffered one or more episodes of cholangitis within the first year after transplantation, compared with the duct-to-duct group (25% versus 9%, $p=0.04$). In parallel with this, the number of admissions for cholangitis was also significantly higher in the Roux-en-Y group (Table 3.3). Of the 17 patients that suffered from cholangitis, 13 (76%) eventually developed NAS.

Only one patient, a 50-year-old man, in whom a duct-to-duct anastomosis was performed, developed *de novo* cholangiocarcinoma in the distal native bile duct, six years after transplantation. The patient died 10 months later due to metastatic disease.

There were no significant differences in the incidence of anastomotic biliary strictures (Table 3.2). The overall incidence of NAS was 2-times higher in the Roux-en-Y group, compared with the duct-to-duct group (45% versus 27%), but this did not reach statistical significance ($p=0.06$). However, more patients in the Roux-en-Y hepatico-jejunostomy group developed late NAS (Table 3.2). When separating early NAS from late NAS, we observed a significantly higher percentage of patients with late NAS in the Roux-en-Y group, compared to the duct-to-duct group (Figure 3.2). The incidence of late NAS was 24% versus 7% at 5 years and 30% versus 7% at 10 years after transplantation ($p=0.01$).

Table 3.2 Comparison of Postoperative Biliary Complications in Patients Undergoing Liver Transplantation for PSC with Duct-to-Duct Biliary Anastomosis versus Roux-Y HepaticoJejunostomy

	Duct-to-Duct (n=45)	Roux-en- Y (n=53)	P-value
Anastomotic Biliary Stricture			
Overall	8 (18%)	11 (20%)	0.14
1-year	4 (9%)	5 (9%)	
3-year	6 (13%)	5 (9%)	
5-year	7 (16%)	6 (11%)	
10-year	8 (18%)	8 (15%)	
Non-anastomotic Biliary Strictures			
Overall	12 (27%)	24 (45%)	0.06
1-year	9 (20%)	8 (15%)	
3-year	12 (27%)	17 (32%)	
5-year	12 (27%)	20 (38%)	
10-year	12 (27%)	22 (42%)	
Biliary Leakage	2 (4%)	3 (6%)	0.07
Cholangitis *	4 (9%)	13 (25%)	0.04
De Novo Cholangiocarcinoma	1 (2%)	0 (0%)	0.28

* Defined as first episode within 1 year after transplantation

Table 3.3 Number of Hospital Admissions for Cholangitis per Patient Undergoing Liver Transplantation for PSC With Duct-to-Duct Biliary Anastomosis Versus Roux-Y Hepatico-Jejunostomy

	Duct-to-Duct (n=45)	Roux-en-Y (n=53)
one	41	40
1 admission	3	6
2 admissions	0	3
3 admissions	0	2
4 admissions	0	1
≥5 admissions	1	1
Total number of admissions	8	28

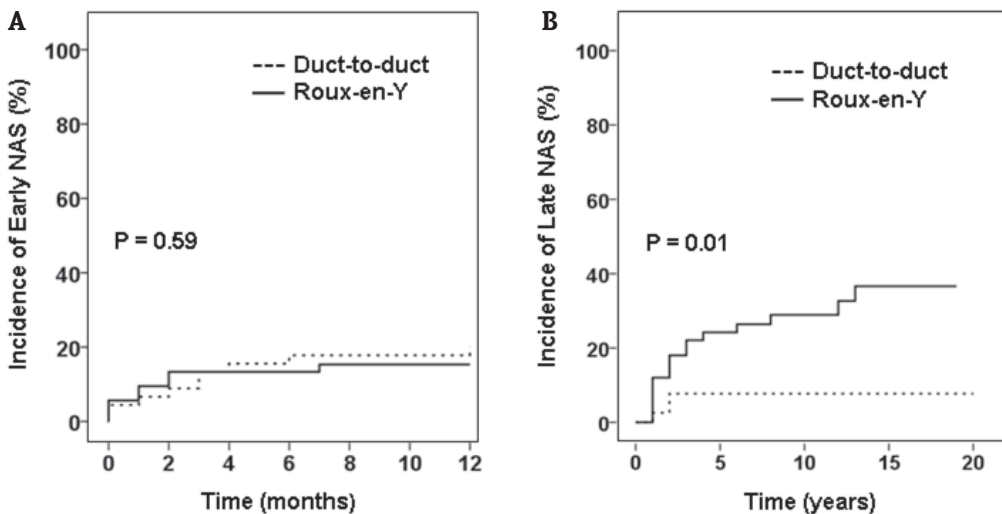


Figure 3.2. Kaplan-Meier estimates of the cumulative incidence of non-anastomotic biliary strictures after liver transplantation in PSC patients based on the method of biliary reconstruction. Panel A: Cumulative incidence of early (≤ 1 year) non-anastomotic biliary strictures. Panel B: Cumulative incidence of late non-anastomotic biliary strictures after orthotopic liver transplantation. Groups were compared using the log rank test.

DISCUSSION

The method of bile duct reconstruction in patients undergoing OLT for PSC remains a topic of debate. While, in general, a duct-to-duct anastomosis is the preferred technique for biliary reconstruction in transplantation, many centers routinely perform a Roux-en-Y hepatico-jejunostomy in patients with PSC. Although several centers have published good short term results of duct-to-duct reconstructions in selected patients with PSC, the long term results of this technique are not well described.

We here report the largest single center study with long-term follow up in 98 patients undergoing OLT for PSC of whom almost 50% received a duct-to-duct anastomosis. The median duration of follow up was 8.2 years, which allowed adequate assessment of long-term consequences. The main finding of this study was a higher rate of late NAS in patients with a Roux-en-Y hepatico-jejunostomy, compared with a duct-to-duct anastomosis. Interestingly, the incidence of late NAS after a Roux-en-Y reconstruction continued to rise beyond 5-years after transplantation. This continuing increase in the cumulative incidence of NAS was not observed after duct-to-duct anastomosis. Roux-en-Y anastomosis was also associated with a significantly higher rate of cholangitis in the first year after transplantation, compared to duct-to-duct reconstruction. In accordance with previous studies, there were no significant differences in general outcome parameters such as patient and graft survival rates.

These findings suggest that recurrent (subclinical) ascending cholangitis, as is seen more often patients with a Roux-en-Y reconstruction, may contribute to the late development of biliary strictures. Roux-en-Y hepatico-jejunostomy results in an open connection between the biliary tract and the bowel lumen, facilitating ascending migration of bacteria and (recurrent) cholangitis. It has been suggested that bacterial colonization of the intrahepatic bile ducts and recurrent (subclinical) cholangitis may contribute to the development of NAS in both PSC and non-PSC patients (15, 16). However, in a large clinical study including 486 liver transplant procedures, our group has previously shown that the higher incidence of NAS after a Roux-en-Y reconstruction in the general liver transplant population can be explained by the more frequent use of this type of reconstruction in patients with PSC (17). The significantly higher rate of NAS observed after Roux-en-Y reconstruction in the current series of patients with PSC, therefore, suggests that recurrent ascending cholangitis associated with this type of reconstruction may result in a higher rate of recurrent PSC after transplantation. Unfortunately, in this retrospective study we could not discriminate between biliary strictures that were due to recurrent PSC or caused by other types of biliary injury and subsequent fibrotic narrowing.

The main reason why most centers continue to prefer a Roux-en-Y biliary reconstruction in patients undergoing OLT for PSC is the assumed higher risk of bile outflow obstruction due to progression of disease and subsequent stricture formation in the distal native bile duct. In addition, the perceived risk of cholangiocarcinoma that may develop in the remnant native bile duct has been a reason to remove as much as possible of the recipient bile duct. In the current series, only two patients with an initial duct-to-duct anastomosis had to be

converted into a Roux-en-Y hepatico-jejunostomy at 9 and 41 months after transplantation. Moreover, the incidence of anastomotic strictures was similar between groups. These findings suggest that the risk of biliary outflow problems due to progression of disease and stricture formation in the native bile duct is rare and should not be used as a reason to perform Roux-en-Y reconstruction.

Our center has been one of the first to report on the successful short-term results of a duct-to-duct anastomosis in patients undergoing OLT for PSC (14). Since our initial publication in 1997 we have continued to perform duct-to-duct anastomoses in patients with PSC whenever possible. This enabled us to study long-term results of this technique in a relatively large cohort. Other single center reports have included much smaller numbers of patients with shorter follow up (9-11). Only one previous study by Damrah et al reported on long-term outcome after transplantation for PSC using either a duct-to-duct or Roux-en-Y anastomosis (8). In this study, the occurrence of NAS is not described in great detail. It is only mentioned that recurrence of PSC was found in 4.8% of patients in the duct-to-duct group versus 10.7% in the Roux-en-Y group. However, graft survival rates at 5 and 10 years were considerably lower compared to those in the current series. Damrah et al reported graft survival rates at 5 and 10-years of 48% and 42% in the duct-to-duct group and 53% and 53% in the Roux-en-Y group (8). Graft survival rates at these time intervals in the current series were 79% and 64% in the duct-to-duct group and 82% and 73% in the Roux-en-Y group. These differences in long-term graft survival make it difficult to compare the two studies.

A retrospective analysis of the UK Transplant database revealed higher 5-year patient and graft survival rates in patients after OLT for PSC with a Roux-en-Y, compared to a duct-to-duct reconstruction (7). These data are in sharp contrast with our findings as well as those of other single center studies (8, 10). The number of biliary strictures in the UK Transplant report was remarkably low: 2% in the Roux-en-Y group versus 8% in the duct-to-duct group. Unfortunately, anastomotic strictures and NAS were not reported separately, and the authors admitted in their report that the low percentages may be explained by under-reporting of biliary complications to UK Transplant as well as a relatively short median follow-up period of 4 years.

It is well known that patients with PSC have a higher risk of developing cholangiocarcinoma, compared to the general population (18-20). The prevalence of cholangiocarcinoma in patients with PSC is around 10% (1). However, it is not well known whether this risk of *de novo*

cholangiocarcinoma persists in the remnant native bile duct after transplantation. The origin of cholangiocarcinoma is assumed to be preceded by bile duct epithelial dysplasia. Whether the occurrence of biliary dysplasia results from immunological factors directed towards the biliary epithelium, alterations in the composition of bile in patients with PSC, or a continuous inflammatory response in these patients is unclear (21, 22). It is also unknown whether removal of as much as possible of recipient bile duct reduces the risk of *de novo* cholangiocarcinoma after transplantation. Unless liver transplantation is routinely combined with a pancreatoduodenectomy, the native bile duct will always remain partly present, regardless whether a duct-to-duct anastomosis or a Roux-en-Y hepatico-jejunostomy is performed. In the current series with a median posttransplant follow up of 8.2 years, we observed one patient (1.0% of all patients) who developed *de novo* cholangiocarcinoma in the native bile duct. In this patient a duct-to-duct reconstruction was performed and cholangiocarcinoma was diagnosed 6 years after OLT. In the UK database analysis, 5 (1.4%) patients were identified who died within three months after OLT due to recurrent cholangiocarcinoma. However, no cases of *de novo* cholangiocarcinoma were noted in this study, including 98 patients with a duct-to-duct anastomosis (7). In addition, no cases of *de novo* cholangiocarcinoma have been described in other single center reports (8-10). Collectively, these data, based on a total of 246 patients with a duct-to-duct anastomosis, suggest that the risk of *de novo* cholangiocarcinoma in the recipient bile duct remnant is very low and not different in patients with duct-to-duct anastomosis or a Roux-en-Y hepatico-jejunostomy.

Apart from a duct-to-duct anastomosis or a hepatico-jejunostomy, other groups have reported the use of choledocho-duodenostomy for biliary reconstruction in patients with PSC (23). However, this method is associated with higher rates of biliary complications. Therefore, we believe a choledocho-duodenostomy should only be performed when formation of a Roux-en-Y loop is difficult or hampered by severe abdominal adhesions or short bowel.

A limitation of our study is the selective usage of a duct-to-duct anastomosis. As mentioned, this technique is only used when certain criteria are met and we certainly would not advocate its routine application in all patients undergoing OLT for PSC. Although this strategy may have introduced a selection bias between the two groups, this does not affect our main conclusion that if a duct-to-duct anastomosis can be performed this is associated with a lower risk of late NAS after transplantation than a Roux-en-Y hepatico-jejunostomy.

In conclusion, this study suggests that the use of duct-to-duct biliary reconstruction in patients with PSC is associated with lower incidences of posttransplant cholangitis and late NAS, compared with Roux-en-Y hepatico-jejunostomy. There is no evidence to suggest that a duct-to-duct anastomosis is associated with a higher risk of cholangiocarcinoma in the remnant recipient bile duct. If technically and anatomically feasible, duct-to-duct anastomosis should be the preferred technique of biliary reconstruction in patients undergoing OLT for PSC.

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